Doxazosin GITS versus standard doxazosin in mild to moderate hypertension

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Abstract

Background: The selective α1-adrenoceptor antagonist doxazosin in both standard formulation and gastrointestinal therapeutic system (GITS) controlled-release formulation is effective for hypertension without having a negative impact on serum lipids. This study was designed to compare the relative efficacy of these two formulations of doxazosin on clinic and ambulatory blood pressure and serum lipids in patients with mild to moderate hypertension.

Methods: Hypertensive patients aged 18–70 years (n=335) were evaluated in a multi-center prospective randomized study. Following a 2-week placebo run-in phase, patients were randomized to receive doxazosin 2 or 4 mg, with dose titration, or doxazosin GITS 4 mg, no dose titration, for 9 weeks.

Results: Both doxazosin formulations reduced clinic diastolic and systolic blood pressure from baseline (P<0.0001). Doxazosin GITS and doxazosin 4 mg had similar blood pressure-lowering effects. Doxazosin GITS reduced sitting diastolic and systolic blood pressure compared with doxazosin 2 mg (P<0.01 for both). A greater proportion of the doxazosin GITS group reached goal blood pressure (<140/90 mm Hg) after 9 weeks compared with the doxazosin 2-mg group. All doses of doxazosin reduced 24-h and daytime (7:00 am to 10:00 pm) ambulatory blood pressure from baseline (all P<0.01). Doxazosin GITS significantly reduced nighttime (10:00 pm to 7:00 am) ambulatory blood pressure from baseline. A neutral effect on serum lipids was observed with doxazosin.

Conclusions: Doxazosin GITS and doxazosin were effective in reducing clinic and ambulatory blood pressure. The GITS formulation reduced the need for dose titration. Both doxazosin formulations were well tolerated.

Keywords: Ambulatory blood pressure; Doxazosin; Gastrointestinal therapeutic system; Hypertension; Serum lipids

1. Introduction

Hypertension, defined as a sustained systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg, and its related complications—stroke, heart failure, and end-stage renal disease—are of major public health concern [1–3]. Several classes of antihypertensive medications have been shown to be effective as therapy, either alone or in combination, for patients with hypertension, and reductions in blood pressure can have significant beneficial effects on morbidity and mortality [2,4].

Doxazosin is a long-acting selective α1-adrenoceptor antagonist that is effective and well tolerated in the treatment of patients with hypertension [5–10]. Doxazosin has also been shown to have a beneficial effect on lipid metabolism after short-term [9] and long-term treatment.
The controlled-release gastrointestinal therapeutic system (GITS) formulation of doxazosin has an enhanced pharmacokinetic profile and drug delivery rate compared with the standard formulation and eliminates the need for slow dose titration to reduce the risk of adverse first-dose effects [12,13].

The objective of this study was to determine the efficacy and safety of doxazosin GITS 4 mg versus standard doxazosin 2 mg and standard doxazosin 4 mg on clinic and ambulatory blood pressure and lipid profile in patients with mild to moderate hypertension.

2. Materials and methods

2.1. Patients

Patients with mild to moderate hypertension were enrolled into the study at four centers in Spain after approval of the protocol by each institution’s human research committee. All patients provided informed consent to participate in the study, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Inclusion criteria for this prospective, multicenter, randomized, double-blind, parallel-controlled trial required patients to be between the ages of 18 and 70 years, to have a mean diastolic blood pressure between 90 and 110 mm Hg, and to have a history of treatment with one or two agents was acceptable. Before study entry; however, previous antihypertensive medication. No dose reduction was permitted. Patients who were unable to tolerate the assigned medication regimen were withdrawn from the study.

The intent-to-treat (ITT) population consisted of all randomized patients in the study that received at least one dose of study medication and had a postbaseline blood pressure value in the active treatment phase, regardless of whether they were protocol violators.

2.2. Study design

Four hundred eighty-six patients at four centers in Spain were screened, and 335 eligible patients were randomized to treatment with doxazosin 2 mg, doxazosin 4 mg, or doxazosin GITS 4 mg. Following a 2-week placebo run-in phase, patients were randomized to receive study medication for 9 weeks. The active treatment phase consisted of a 3-week fixed-dose titration schedule according to assigned treatment group and a 6-week maintenance period at the titrated dose. Patients began this phase with either doxazosin 1 mg or doxazosin GITS.

For patients randomized to doxazosin 2 mg, the dose of doxazosin was increased from 1 to 2 mg at 1 week after randomization unless prevented by adverse events (AEs). Patients randomized to doxazosin 2 mg underwent dummy titration at the end of week 3. For patients randomized to doxazosin 4 mg, the dose of doxazosin was increased from 1 to 2 mg then from 2 to 4 mg at weeks 1 and 3, respectively. For patients randomized to doxazosin GITS, the dose remained the same (4 mg) during the entire study period. These patients underwent dummy titration steps at the end of weeks 1 and 3.

Study visits occurred on weeks −2, 0, 1, 3, 5, and 9. For all visits after the initial screening, patients were evaluated approximately 24 h after the previous day’s dose of study medication. No dose reduction was permitted. Patients who were unable to tolerate the assigned medication regimen were discontinued and were not replaced.

2.3. Assessments

Efficacy was assessed using clinic and ambulatory blood pressure measurements. Assessment of treatment equivalence between the two 4-mg doxazosin formulations was based on the change from baseline in sitting systolic blood pressure at week 9. Changes from baseline in sitting diastolic blood pressure, systolic blood pressure, mean blood pressure, and heart rate were evaluated on weeks 1, 3, 5, and 9 in the ITT population. Changes from baseline to week 9 in ambulatory blood pressure monitoring during diurnal (7:00 am to 10:00 pm), nocturnal (10:00 pm to 7:00 am), and 24-h periods were conducted based on single measurements but not on the summary statistics. The investigators decided on inclusion of patients into the study after review of the ambulatory blood pressure monitoring summary statistics. Changes from baseline to week 9 in lipid parameters (i.e., total cholesterol, low-density lipoproteins, high-density lipoproteins, and triglycerides) were also evaluated.
A complete medical history and physical examination was conducted at both the first and last study visit, including electrocardiography and laboratory parameters. AEs were recorded at each visit based on investigator and patient reports and treatment-emergent AEs and are summarized in terms provided in the World Health Organization Adverse Reaction Terminology dictionary for classification.

2.4. Statistical analysis

All efficacy response variables were analyzed using analysis of covariance. All statistical tests of significance were two-sided and performed at the 5% significance level. In addition to the treatment group, the baseline and center covariates were included in efficacy models. Treatment was fitted as a categorical variable, with the reference group being the doxazosin 2-mg treatment group. In all analyses, inferences about treatment effects were based on this model. For continuous measurements of data from patients who withdrew from the study, the last observation carried forward was applied to analyze the ITT population. There was no adjustment made to nominal significance levels to account for multiple secondary end points. Standard methods of model checking were used to investigate the appropriateness of each analysis. All statistical outputs were generated using SAS® version 8.2.

3. Results

3.1. Patients and baseline characteristics

Three hundred thirty-five patients were randomized to receive doxazosin GITS (n=114), doxazosin 2 mg (n=111), or doxazosin 4 mg (n=110). Four patients (two from the doxazosin 2-mg group and two from the doxazosin GITS group) were excluded from the analyses because they did not have a postbaseline value in the active treatment phase. Therefore, the efficacy or ITT analysis included 331 patients, whereas the safety analysis included all 335 patients who were randomized.

Patient demographic characteristics for the ITT population are provided in Table 1. The mean age of patients was similar among groups and was 51 years for the entire patient population. There were more men (54%) than women. Mean sitting blood pressure at baseline was 160/101 mm Hg, and ambulatory diurnal blood pressure was 148/95 mm Hg. No differences in baseline clinic or diurnal blood pressure were observed among groups.

3.2. Efficacy

3.2.1. Doxazosin GITS reduces the need for dose titration

By week 1, patients receiving doxazosin GITS, compared with patients receiving doxazosin 1 mg (both standard doxazosin groups were in the dose titration period at week 1), had statistically significant decreases in sitting diastolic blood pressure (−5.8 vs. −3.8 mm Hg; P=0.0026), systolic blood pressure (−7.5 vs. −5.1 mm Hg; P=0.0430), and sitting mean blood pressure (−6.3 vs. −4.1 mm Hg; P=0.0042). By week 3, the decrease in sitting systolic blood pressure and mean blood pressure in the doxazosin GITS group was greater than the doxazosin 2-mg group (−9.4 vs. −6.9 mm Hg, −7.8 vs. −6.1 mm Hg, respectively) and remained statistically significant through week 9 (P<0.05). The difference between groups in sitting diastolic blood pressure at week 3 approached significance (P=0.0507), whereas standing blood pressure values were

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<th>Table 1</th>
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<tr>
<td></td>
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<tr>
<td>Men, n (%)</td>
<td>60 (54)</td>
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<tr>
<td>Women, n (%)</td>
<td>52 (46)</td>
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<td>Mean age, years (S.D.)</td>
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<tr>
<td>Mean baseline standing BP, mm Hg (S.D.)</td>
<td>156.0±15.3/</td>
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<tr>
<td>Mean baseline 24-h ambulatory BP, mm Hg (S.D.)</td>
<td>142.6±9.9/</td>
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<td>BP, mm Hg (S.D.)</td>
<td>91.5±6.6</td>
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<tr>
<td>Mean baseline diurnal ambulatory BP, mm Hg (S.D.)</td>
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<tr>
<td>BP, mm Hg (S.D.)</td>
<td>95.7±6.6</td>
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<tr>
<td>Mean baseline night ambulatory BP, mm Hg (S.D.)</td>
<td>132.6±13.0/</td>
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<tr>
<td>BP, mm Hg (S.D.)</td>
<td>82.6±8.7</td>
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</table>

BP= blood pressure; DOX= standard doxazosin; DOX GITS= doxazosin gastrointestinal therapeutic system, controlled-release formulation; S.D.= standard deviation.

a n=111.
b n=108.
c n=329.
not different between groups. By week 5, the decrease in sitting diastolic blood pressure in the doxazosin GITS group (−6.8 mm Hg) was greater than that in the doxazosin 2-mg group.

Fig. 1. Changes from baseline in sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP) after treatment with doxazosin gastrointestinal therapeutic system (DOX GITS) or standard doxazosin (DOX) over the 9-week dosing period. *P<0.01; †P=0.0507. Mean±S.D. sitting SBP at 9 weeks for all groups were: DOX GITS, 144.1±14.8; DOX 4 mg, 144.5±12.8; DOX 2 mg, 150.3±12.1. Sitting DBP at 9 weeks for all groups were: DOX GITS, 91.3±9.2; DOX 4 mg, 90.4±8.4; DOX 2 mg, 95.4±8.2.

Fig. 2. Percentage of patients achieving goal blood pressure (i.e., sitting systolic blood pressure ≤140 mm Hg and diastolic blood pressure ≤90 mm Hg) at the last visit in the intent-to-treat population. A statistically significant treatment effect was observed (*P<0.0001) in the doxazosin gastrointestinal therapeutic system (DOX GITS) 4-mg group compared with the standard doxazosin (DOX) 2-mg group. No significant differences were noted between the DOX GITS and DOX 4-mg groups.

Fig. 3. Effects of doxazosin formulations on clinic blood pressure. (A) Adjusted mean change from baseline to the final visit in sitting diastolic blood pressure (DBP). A statistically significant decrease was observed (P=0.0002) in the doxazosin gastrointestinal therapeutic system (DOX GITS) group compared with the standard doxazosin (DOX) 2-mg group. (B) Adjusted mean change from baseline to the final visit in sitting systolic blood pressure (SBP). A statistically significant decrease was observed (P=0.006) in the DOX GITS group compared with the DOX 2-mg group. (C) Adjusted mean change from baseline to the final visit in sitting mean blood pressure (BP). A statistically significant treatment effect was observed (P=0.0004) in the DOX GITS group compared with the DOX 2-mg group. NS=not significant.
Because the inclusion criteria for ambulatory blood pressure monitoring differed from other analyses, N=287 for this analysis.

Data are presented as unadjusted mean change from baseline (±S.D.). Statistical comparisons were based on adjusted mean change from treatment center baseline. DOX=standard doxazosin; DOX GITS=doxazosin gastrointestinal therapeutic system, controlled-release formulation; NS=not significant; S.D.=standard deviation.

* P<0.0001.
† P<0.05.
‡ P<0.001.
§ P<0.01.

group (−4.5 mm Hg) and remained so at week 9. By week 5, changes in blood pressure measures were similar between doxazosin GITS and doxazosin 4 mg and similar to that observed on week 3 with doxazosin GITS. Fig. 1 shows the changes in sitting diastolic blood pressure and systolic blood pressure over the course of treatment.

3.2.2. Reaching goal blood pressure

A significantly greater proportion of patients in the doxazosin GITS group reached goal blood pressure (≤140/90 mm Hg) by the end of the study compared with the doxazosin 2-mg group (P<0.0001, Fig. 2). There was no significant difference between the doxazosin GITS and doxazosin 4-mg groups in the percentage of patients at goal blood pressure.

3.2.3. Reduction of blood pressure

By the end of the study, doxazosin GITS and doxazosin 4 mg were similarly effective in reducing sitting diastolic blood pressure from baseline (Fig. 3A). The mean change in diastolic blood pressure from baseline to the final visit was statistically greater in patients receiving doxazosin GITS than doxazosin 2 mg.

Adjusted mean change from baseline in sitting systolic blood pressure was similar in patients receiving doxazosin GITS and doxazosin 4 mg. There was a statistically significant difference between the doxazosin 2-mg group and the doxazosin GITS group (P<0.0004; Fig. 3B). Reductions from baseline in sitting mean blood pressure were similar in patients receiving doxazosin GITS and doxazosin 4 mg, and the response in the doxazosin GITS group was statistically greater than that in the doxazosin 2-mg group (P<0.0004; Fig. 3C).

3.2.4. Ambulatory blood pressure monitoring—24-h blood pressure control

The adjusted mean changes from baseline in ambulatory blood pressure are presented in Table 2. Doxazosin treatment resulted in significant reductions in 24-h and daytime (7:00 am to 10:00 pm) ambulatory blood pressure from baseline in all groups. Doxazosin GITS also significantly reduced nighttime (10:00 pm to 7:00 am) ambulatory blood pressure from baseline. Compared with the other groups, doxazosin GITS induced a significantly greater reduction in
nighttime ambulatory systolic blood pressure and mean blood pressure.

3.2.5. Serum lipids

In this short-term study, doxazosin had a small positive effect on serum lipids that was not statistically significant (Table 3).

3.3. Safety and tolerability

All formulations of doxazosin were well tolerated. Treatment with doxazosin GITS and standard doxazosin resulted in similar total AEs, although fewer patients reported AEs in the GITS group. The distribution of treatment-related treatment-emergent AEs by severity and association with study drug is presented in Table 4. Most reported AEs were mild to moderate in severity. The most common AEs were headache and dizziness. Seven (6%) patients in the doxazosin GITS group, seven (6%) patients in the doxazosin 2-mg group, and four (4%) patients in the doxazosin 4-mg group withdrew from the study as a result of treatment-emergent AEs.

4. Discussion

The GITS controlled-release formulation of doxazosin was developed with the objective of maintaining efficacy, improving tolerance, and eliminating the need for titration to the therapeutic dose. In this study, doxazosin GITS and doxazosin 4 mg produced equivalent reductions in clinic blood pressure, and doxazosin GITS produced a significantly greater reduction than doxazosin 2 mg in all blood pressure measures. In addition, doxazosin GITS was more effective than either dose of the standard formulation in reducing nighttime ambulatory systolic blood pressure and mean blood pressure.

During the first weeks of the study, the GITS formulation lowered blood pressure more than the standard formulation, underscoring the therapeutic effects of the initial dose of doxazosin GITS 4 mg. Patients in the doxazosin 4-mg group did not receive a dose equivalent to that received by the doxazosin GITS group until week 5. Furthermore, there was no difference among the treatment groups in the incidence of AEs. These data demonstrate that doxazosin GITS provided a more rapid blood pressure benefit to patients and did not require a dose titration phase. The data were consistent with other studies indicating that treatment with doxazosin GITS eliminated the need for dose titration. In a combined analysis of two randomized double-blind clinical trials comparing doxazosin GITS and standard doxazosin in patients with mild to moderate hypertension, Os and Stokke [13] reported that doxazosin GITS and standard doxazosin provided equally effective blood pressure reduction and that the GITS formulation of doxazosin eliminated the need for titration in most patients. This benefit with doxazosin GITS allows patients to receive therapeutic doses at drug initiation and with a level of tolerance similar to that with titrated standard doxazosin [13,14].

The 24-h blood pressure control of doxazosin GITS, including significant reductions in nighttime blood pressure, supports the drug delivery advantages of the GITS formulation to maintain a balanced action over 24 h. As described by Chung et al.,[14] doxazosin GITS produces a more gradual decline in plasma concentrations during the 24 h postdose than is observed using the standard formulation. This more gradual decline in plasma concentrations most likely was responsible for the significant reduction in nighttime blood pressure observed with doxazosin GITS vs. doxazosin standard. The GITS formulation also avoids the rapid increases in drug plasma concentration observed with standard doxazosin and may be the basis of its tolerability at higher initial doses [13,14]. Whether this property of doxazosin GITS translates into improved cardiovascular outcomes is uncertain given the novelty of this formulation.

The effect of doxazosin GITS on 24-h ambulatory blood pressure profiles in hypertensive patients have been recently reported by Lemmer and Nold [15]. They demonstrated that 4 mg doxazosin GITS for 6 weeks significantly reduced daytime and nighttime systolic blood pressure and diastolic blood pressure as well as the rhythm-adjusted mean systolic blood pressure and diastolic blood pressure, maximum systolic blood pressure and diastolic blood pressure, and minimum systolic blood pressure. No significant effect on
studies [14]. However, even with the standard formulation effects on blood pressure as suggested by pharmacokinetic studies [14]. The recently published report of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) has raised concerns regarding the role of doxazosin in hypertensive treatment [18,19]. Doxazosin standard was originally included in ALLHAT to compare the effects of monotherapy with newer drugs such as doxazosin, amlopidine, and lisinopril with the diuretic chlorthalidone in hypertensive patients over a 4- to 8-year period [20]. An interim review of data indicated that the incidence of CHF was significantly higher in the doxazosin arm compared with the diuretic arm of the study and the doxazosin arm was discontinued early [18,21]. However, ALLHAT was not designed to allow assessment of whether doxazosin was better or worse than placebo because it was not a placebo-controlled trial and the trial was not designed to test the efficacy of doxazosin as part of a multidrug regimen [21]. Furthermore, no significant increase in the primary end points of combined fatal coronary heart disease or nonfatal MI were observed between the diuretic and doxazosin treated groups [18]. Several aspects of the discontinuation of the doxazosin arm of ALLHAT have been controversial. These aspects include the fact that the CHF diagnosis was not standardized or well validated [22–24] and that systolic blood pressure in the diuretic arm of the study was approximately 2–3 mm Hg lower than in the doxazosin arm. This blood pressure gradient alone may have been able to explain the benefit seen in the diuretic treated patients [4].

Current hypertension treatment guidelines suggest several classes of antihypertensive agents, including thiazide-type diuretics, as first-line treatment options, and many studies, including ALLHAT, have documented that most patients require two or more drugs to lower blood pressure to acceptable levels [2,3,19,25]. Combination therapy with approved antihypertensive medications, including doxazosin, may help to achieve blood pressure goals [2,3].

5. Conclusions

Doxazosin GITS and doxazosin 4 mg were similarly effective in reducing the clinic and ambulatory blood pressure of patients with mild to moderate hypertension without adversely effecting serum lipid profiles. The earlier and significantly greater blood pressure reduction observed with the GITS formulation indicates that it may be a better treatment choice versus the standard formulation in this patient population. Doxazosin GITS provided patients with a therapeutic dose sooner and eliminated the need for dose titration.

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References